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Review article

Review on the comparison of effectiveness between denosumab and bisphosphonates in post-menopausal osteoporosis

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Abstract

Objective: Osteoporosis is a rapidly rising cause of concern for elderly patients. Various classes of drugs are available in the market. Bisphosphonates are considered as a first-line therapy for the prevention and treatment. Denosumab is an antiresorptive agent which is a RANK ligand inhibitor. There is a scarcity of comparison between these two classes of drugs. The aim of this study is to compare efficacy of Bisphosphonates and Denosumab in various parameters.

Materials and methods: Literature search was done for randomized controlled trials (RCTs) comparing bisphosphonates with denosumab. RCTs with a treatment period of at least one year with a baseline bone mineral density (BMD) and bone turnover markers (BTM) and follow up values at one year were included in the study. All included studies were also analysed for complications. The study has also been registered in PROSPERO International prospective register of systematic reviews.

Results: A total of five RCTs were identified providing data on 3751 participants. In all five studies, the BMD changes at both hip and spine were statistically significant in favour of denosumab. Result was similar in three studies that studied BMD changes at the wrist. Denosumab also produced significant reduction in BTM as early as one month, but at one year there was no difference compared to the bisphosphonates. There was no statistically significant differences in the complication rates.

Conclusion: Though both bisphosphonates and denosumab were effective with similar side effects, the latter was statistically superior in increasing the BMD and reducing the BTM.

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Keywords: Denosumab; Bisphosphonates; Post-menopausal osteoporosis; Bone mineral density; C-telopeptide

1. Introduction

Postmenopausal osteoporosis is a disease with features of reduction in the mass of bone, and microscopic changes in the architecture that results in impaired strength of the bone [1]. After menopause, osteoclastic activity exceeds osteoblastic activity. This results in increased bone resorption which leads to an overall reduction of bone mass. This in turn increases skeletal fragility and risk of developing fractures [2]. Therefore the objective of treatment is to increase bone mass by altering the balance of bone remodelling. Most currently available drugs used to treat osteoporosis such as calcitonin, raloxifene and bisphosphonates, acts as inhibitors to bone resorption.

The two main properties of bisphosphonates resulting in their efficacy are the ability to strongly bind to bone mineral and the inhibition of mature osteoclasts [3]. Once the bisphosphonate is strongly attached to bone, this results in

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selective uptake by the bone mineral. After this, the bisphosphonates act at the sites of bone resorption by entering and inhibiting the mature osteoclastic cells.

Receptor activator of nuclear factor kappa-B ligand (RANKL), a cytokine secreted by bone marrow stromal cells, osteoblasts and T cells, is essential to induce osteoclast differentiation [4]. In post-menopausal osteoporosis with estrogen deprivation there is raised expression and production of RANKL, resulting in increased osteoclast activation and increased bone resorption. Reducing the number of osteoclasts by decreasing differentiation of precursor cells is one of the treatment modalities of hyper-resorptive bone diseases. Denosumab is one such fully human monoclonal antibody that can bind and inhibit RANKL.

There are numerous studies on the efficacy of bisphosphonates and other medications available for osteoporosis including denosumab. But there are very few randomised controlled trials (RCT) directly comparing bisphosphonates and denosumab. The aim of this systematic review was to identify studies that simultaneously compared bisphosphonates and denosumab and to analyse the efficacy in various parameters.

2. Materials and methods

Search Strategy: A search was done in several databases such as Pubmed Central, Cochrane CENTRAL and MEDLINE. The search was restricted to articles in English language. The search terms used were osteoporosis, post-menopausal, denosumab, bisphosphonates, bone mineral density and C-telopeptide. A filter for RCTs was also used. The Cochrane handbook of systematic reviews of interventions was referred to identify any discrepancies and biases in randomization, allocation concealment, blinding and missing data in the included RCTs [5].

Inclusion criteria: All RCTs directly comparing bisphosphonates with denosumab in post-menopausal osteoporosis were included. Only fully published reports with initial and final bone mineral density (BMD) and bone turnover markers (BTM) were included. CONSORT check list was used to critically appraise the included studies and all the studies fulfilled the criteria.

Statistical analysis: Data extracted included study design, selection criteria, population demographics, type of intervention, initial and final BMD, initial and final BTM as well as complications if any. Results of all the included studies were described in a table format. Key outcomes were percentage changes in BMD, BTM and complications.

3. Results

A total of six RCTs were identified. In one study, the participants had used denosumab for a long period and then stopped before restarting the therapy [6]. This RCT was excluded from the current study. A total of five RCTs were identified with a total of 3751 participants. The characteristics of the included studies are summarized in Table 1. Three studies compared denosumab with alendronate [7–9] and one study each for denosumab vs. risedronate [10] and denosumab vs. ibandronate [11]. All studies were checked to identify any discrepancies and biases in randomization, allocation concealment and blinding based on CONSORT checklist. No possible bias was found.

In one included RCT, subjects received variable doses of denosumab, viz. 6, 14 or 30 mgs subcutaneously (s/c) every three months or 14, 60, 100 or 210 mgs s/c every six months [7]. In all the other studies, subjects received denosumab in a dose of 60 mg s/c every six months.

3.1. Bone mineral density

Baseline BMD in each of the study was noted for both the groups of subjects. All the five included studies recorded BMD changes at the lumbar spine and hip. In addition to this, four of the studies recorded BMD changes at the femoral neck and three studies at the distal radius. All the five studies reported improvement in BMD at the lumbar spine and hip after treatment in both groups but the improvement was statistically significant in favour of denosumab. Four studies reported statistically significant improvement in BMD at the femoral neck in favour of denosumab. Three studies also reported statistically significant improvement in BMD at the distal radius, again in favour of denosumab. The results are shown in Table 2.

Table 1
Characteristics of included studies.

Study	Study design	Drugs	Dosing	Number of patients	Age of patients in years (SD)	Treatment duration (Months)
Lewiecki EM et al. J Bone Miner Res. 2007 [7]	Randomized	Denosumab	Varying doses s/c every 3 or 6 months	319	62.3 (8.0)	24
	Double blind	Alendronate	70 mgs orally per week	47	62.8 (8.2)	
Brown JP et al. J Bone Miner Res. 2009 [8]	Randomized	Denosumab	60 mgs s/c every 6 months	594	64.1 (8.6)	12
	Double blind	Alendronate	70 mgs orally per week	595	64.6 (8.3)	
Nakamura T et al. J Clin Endocrinol Metab. 2014 [9]	Randomized	Denosumab	60 mgs s/c every 6 months	414	69.9 (7.4)	24
	Double blind	Alendronate	35 mgs orally per week	204	70.2 (7.3)	
Roux C et al. Bone. 2014 [10]	Randomized	Denosumab	60 mgs s/c every 6 months	422	67.8 (7.0)	12
	Open label	Risedronate	150 mgs orally per month	402	67.7 (6.8)	
Recknor C et al. Obstet Gynecol. 2013 [11]	Randomized	Denosumab	60 mgs s/c every 6 months	398	67.2 (8.1)	12
	Open label	Ibandronate	150 mgs orally per month	356	66.2 (7.8)	

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Table 2
Bone mineral density baseline values and changes following treatment.

Study	Drugs	Baseline BMD lumbar spine	Change in BMD lumbar spine	Baseline BMD hip	Change in BMD hip	Baseline BMD femoral neck	Change in BMD femoral neck	Change in BMD distal radius
Lewiecki EM et al. J Bone Miner Res. 2007 [7]	Denosumab	−2.0[a]	8.9%	–	4.8%	–	–	1.2%
	Alendronate	−2.0[a]	6%	–	3%	–	–	1%
			p: <0.001		p: <0.001			p: <0.001
Brown JP et al. J Bone Miner Res. 2009 [8]	Denosumab	−2.57 ± 0.75[b]	5.3%	−1.75 ± 0.79[b]	3.5%	–	2.4%	1.1%
	Alendronate	−2.57 ± 0.75[b]	4.2%	−1.69 ± 0.81[b]	2.6%	–	1.8%	0.6%
			p:<0.0001		p:<0.0001		p:<0.0001	p:<0.0001
Nakamura T et al. J Clin Endocrinol Metab. 2014 [9]	Denosumab	−2.78 ± 0.89[b]	9.1%	−2.01 + −0.79[b]	4.6%	−2.38 + −0.70[b]	4%	0.5%
	Alendronate	−2.69 ± 0.94[b]	7.5%	−1.96 + −0.79[b]	3.6%	−2.29 + −0.71[b]	2.9%	-0.2%
			p: <0.05		p: <0.05		p: <0.05	p: <0.05
Roux C et al. Bone. 2014 [10]	Denosumab	−2.2 ± 1.2[b]	3.4%	−1.6 ± 0.9[b]	2%	−1.9 ± 0.8[b]	1.4%	–
	Risedronate	−2.3 ± 1.1[b]	1.1%	−1.6 ± 0.8[b]	0.4%	−1.9 ± 0.7[b]	0%	–
			p: <0.001		p: <0.001		p: <0.001	
Recknor C et al. Obstet Gynecol. 2013 [11]	Denosumab	−2.5 ± 0.9[b]	4.1%	−1.8 + −0.7[b]	2.3%	−2.1 + −0.7[b]	1.7%	–
	Ibandronate	−2.5 ± 0.8[b]	2%	−1.8 + −0.7[b]	1.1%	−2.1 + −0.7[b]	0.7%	–
			P: <0.001		P: <0.001		P: <0.001	

[a] Mean values.
[b] Mean ± standard deviation.

3.2. Bone turnover markers

Four of the included trials have reported baseline values of the BTM (C-telopeptide), and the percentage in reduction at one month and six months after initiation of treatment [8–11]. All four trials have found denosumab statistically superior to bisphosphonates at one month and three studies have shown a similar superiority at six months. The results are shown in Table 3. However one trial [9] reported that at six months of treatment there was no difference between the two groups and another trial [8] reported that at 12 months of treatment there was no difference between the two groups ($p = 0.52$).

3.3. Complications

The various reported complications include arthralgia, upper respiratory tract infections, nasopharyngitis, clinical fractures and osteoporotic fractures. However there was no statistical difference between the two groups. The results are summarized in Table 4.

One study [7], reported the incidence of dyspepsia (denosumab: 10.5% vs. alendronate: 26.1%) and nausea (denosumab: 11.1% vs. alendronate: 21.7%). Though these gastrointestinal side effects were more in the alendronate group, they were not statistically significant. One study [8] described pyelonephritis (denosumab: 0.2% vs. alendronate: 0%) and another study [11] described the incidence of urinary tract infection (denosumab: 3.4% vs. ibandronate: 4.6%). Again, there was no statistical significance between the groups. Overall fracture rates and occurrence of osteoporotic fractures have been described in four studies with no statistical significance between the groups. One study found no complications in fracture healing in both the groups [9].

There was also no statistical significance between the dropout rates because of adverse events, in three of the included studies [7–9].

4. Discussion

RANK receptors are present on osteoclasts and their precursor cells. Denosumab prevents the interaction of RANKL with these receptors. This results in blocking the formation, functional ability, and survival of osteoclastic cells [4]. On the other hand, bisphosphonates bind to the calcium

Table 3
Bone turnover markers baseline values and changes following treatment.

Study	Drugs	Baseline C-telopeptide (ng/mL)	Reduction in C-telopeptide at 1 month	Statistical Significance	Reduction in C-telopeptide at 6 months	Statistical Significance
Brown JP et al. J Bone Miner Res. 2009 [8]	Denosumab	0.705	89%	Significant	77%	Significant
	Alendronate	0.654	61%	P < 0.0001	73%	P < 0.0001
Nakamura T et al. J Clin Endocrinol Metab. 2014 [9]	Denosumab	0.64	70.9%	Significant	67	Not significant
	Alendronate	0.61	43%	P < 0.05	66.3%	
Roux C et al. Bone. 2014 [10]	Denosumab	0.52	77.7%	Significant	60.6%	Significant
	Risedronate	0.53	17%	P < 0.0001	22.5%	P < 0.0001
Recknor C et al. Obstet Gynecol. 2013 [11]	Denosumab	0.4	81.1%	Significant	60.5%	Significant
	Ibandronate	0.4	35%	P < 0.001	45.4%	P < 0.001

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Table 4
Common complications described in most studies.

Study	Lewiecki EM et al. J Bone Miner Res. 2007 [7]		Brown JP et al. J Bone Miner Res. 2009 [8]		Nakamura T et al. J Clin Endocrinol Metab. 2014 [9]		Roux C et al. Bone. 2014 [10]		Recknor C et al. Obstet Gynecol. 2013 [11]	
Medication used	D	BP	D	BP	D	BP	D	BP	D	BP
Arthralgia	19.1%	23.9%	12.6%	9.6%	–	–	4%	4.4%	6.1%	5.6%
URTI	24.2%	23.9%	6.1%	4.4%	–	–			5.1%	2.2%
Nasopharyngitis	–	–	–	–	44.4%	38.4%	3.5%	4.2%		
All clinical fractures	6.7%	4.3%	4%	3.2%	–	–	4.4%	3.5%	3.6%	3.2%
Osteoporotic fractures	3.8%	4.3%	3%	2.2%	–	–	2.5%	1.4%	1.5%	1.1%
Discontinue at 1 year due to AE	1.6%	0%	0.5%	0.7%	1.1%	0.8%	–	–	–	–

D: Denosumab, BP: Bisphosphonates, URTI: Upper Respiratory Tract Infection, AE: Adverse effects.

hydroxyapatite present in bone and reduce bone resorption by affecting the function and survival of osteoclasts. But they do not affect the formation of osteoclasts [3].

For the diagnosis of osteoporosis, analysis of bone mineral density using dual-energy X-ray absorptiometry (DXA) is the gold standard [12]. All the included studies in this review showed increase in BMD at lumbar spine, hip, femoral neck and distal radius in favour of denosumab as shown in Table 2.

BMD is a commonly used marker to assess efficacy of treatment of osteoporosis. However it is not useful to repeat the BMD within an interval of 2 years because the effect of treatment is relatively small compared to the precision of the test. There is also no precise and consistent relationship between a given increase in BMD and a specific decrease in fracture risk with osteoporosis therapy. BTMs are a non-invasive way of assessing the efficacy of the treatment. Biochemical analysis can be used to monitor bone metabolism. Enzymes and proteins are released during bone formation and bone resorption results in release of products of degradation. Analysing these biochemical markers can result in a specific and sensitive assessment of the rate of bone formation and bone resorption. These are C-terminal telopeptide of type 1 collagen (CTX) for bone resorption, and procollagen type 1 N propeptide (P1NP) for bone formation [13]. These markers usually fall by around 40% within 3 months of commencing bisphosphonate therapy. This is also usually followed by a reduction in the levels of bone formation markers during the next 6–12 months [14]. If the BTM levels do not reduce after antiresorptive therapy, it could be a result of the patient not complying with therapy, failure of absorption or an undetected cause of secondary osteoporosis. Denosumab has been shown to produce a very rapid fall and suppression of resorption markers, with a slower fall in formation markers [15]. Our study confirmed this finding with all the included studies showing a very rapid fall in resorption markers.

Denosumab has been shown to be associated with a significant reduction in the risk of vertebral, hip, and nonvertebral fractures compared to placebos in postmenopausal women with osteoporosis [16]. All the included studies in this review found no statistical significance between the groups. However, the limitation of this study was that none of the included studies were powered to compare fracture rates between the groups. Previous studies in postmenopausal women have reported a greater incidence in serious adverse events of infection for denosumab compared with placebo [6,17]. This current study did not observe any statistical significance between the groups.

In conclusion, increasing BMD by decreasing bone resorption through the inhibition of RANKL is an alternative approach to the treatment of osteoporosis. Denosumab is a human monoclonal antibody that can achieve this result. Use of Denosumab results in significant increase in BMD and reduction in the BTMs compared to various bisphosphonates. There was also no statistically significant complications.

Conflict of interest

We, the authors of this study declare that there is no financial conflicts of interest or other interests that may influence the manuscript. We have not received any funding for the work undertaken.

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